REMARKS

A Petition for Extension of Time is being concurrently filed with this Amendment. Thus, this Amendment is timely filed.

Applicants respectfully request the Examiner to reconsider the present application in view of the foregoing amendments to the claims and the following remarks.

Status of the Claims

Claims 2-15 are currently pending in the present application. The Office Action is non-final. Claim 1 has been cancelled without prejudice or disclaimer. Claims 2-6, 8 and 10 have been amended without prejudice or disclaimer. Claims 11-15 are new. No new matter has been added by way of new or amended claims because the new and amended claims are supported by the present specification and the original claims. The new and amended claims further define and clarify the structure of the present invention.

Additionally, support for item 5 of claim 2 can be found on page 17, lines 23-28, Examples 11-15, as well as Figures 15-18 of the present specification. In Figure 17, "compound 10" is an embodiment wherein the dicholoroacetyl group is introduced via amino acetylenic linker. Claim 5 was amended into independent form. Claims 11 and 12 depend upon claim 5 and support can be found within original claims 3 and 4. Thus, no new matter has been added.

Based upon the above considerations, entry of the present amendment is respectfully requested.

Claim Objections

The Examiner states that claims 4-10 were objected for improper multiple dependent claim form.

Applicants have amended claims 2-6, without prejudice or disclaimer, to obviate this objection.

Applicants respectfully request reconsideration, withdrawal of the objection and subsequent examination of claims 4-10 on their merits.

Rejection Under 35 U.S.C. § 102(b), Anticipation

Claim 1 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Ohtsuki *et al.*, *"Unnatural Base Pairs for Specific Transcription,"* Proc. Natl. Acad. Sci., Vol. 98, (2001), pages 4922-4925 (hereinafter "Ohtsuki *et al.*"). The Examiner states that Ohtsuki *et al.* discloses the unnatural nucleobase m^5y in which the R group substituted at the fifth position is a methyl group.

Applicants have cancelled claim 1, without prejudice or disclaimer of the subject matter herein, thus obviating the present rejection.

Applicants respectfully request reconsideration and withdrawal of the present rejection.

Rejection Under 35 U.S.C. § 103(a), Obviousness

Claims 1-3 stand rejected under 35 U.S.C. § 103(a) as being unpatentable Froehler *et al.*, U.S. Patent No. 6,447,998, U.S. Patent No. 6,495,672 or US Patent Publication No. 2003/0120065 (hereinafter "Froehler *et al.*").

Claim 1 has been cancelled herein without prejudice or disclaimer, thus obviating the rejection as to this claim.

The Examiner asserts that Froehler *et al.* discloses 2-aminopyridine and 2-pyridone C-nucleosides and oligonucleotides containing the subject nucleosides. The Examiner provides an example structure from Froehler *et al.* (Formula II) and compares it to the formula found in Figure 3. The Examiner initially states that the instantly claimed nucleosides or nucleotides comprise a structure that differs from the prior art to the extent that the positions at which the ribose and the alkynyl groups attach to the pyridine ring are different. But based on the comparison, the Examiner further suggests that it would have been obvious to seek alternative nucleobases to vary the positions of the substituents in the pyridine ring to produce another nucleobase to be used for the same purpose, namely for incorporation into nucleic acid molecules. Applicants respectfully traverse the rejection as to the remaining claims as set forth herein.

Graham v. John Deere, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), has provided the controlling framework for an obviousness analysis. A proper analysis under § 103(a) requires

consideration of the four *Graham* factors of: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims that are at issue; resolving the level of ordinary skill in the pertinent art; and evaluating any evidence of secondary considerations (e.g., commercial success; unexpected results). 383 U.S. at 17, 148 USPQ at 467.

The teaching, suggestion, motivation test is a valid test for obviousness, but one which cannot be too rigidly applied. *See KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385, 1395 (U.S. 2007). While the courts have adopted a more flexible teaching/suggestion/motivation (TSM) test in connection with the obviousness standard based on the *KSR v. Teleflex* case which involved a mechanical device in a relatively predictable technological area, it remains true that, despite this altered standard, the courts recognize inventors face additional barriers in relatively unpredictable technological areas as noted in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) (since TSM test can provide helpful insight if it is not applied as rigid and mandatory formula, and since, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led chemist to modify known compound, in particular manner, in order to establish *prima facie* obviousness of new compound).

Recently, the U.S.P.T.O. published a set of Obviousness Guidelines titled: "Examination Guidelines for Determining Obviousness under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*" (*See*, Fed. Reg. 72(195):57526-57535, October 10, 2007). This publication provides a review of the factors to be considered under the test announced in the *Graham v. John Deere* holding. These Obviousness Guidelines re-affirm the validity of the TSM test in determining obviousness, as well as the factor test of *Graham v. John Deere*.

The present invention according to claims 2-4 is directed to a nucleoside or nucleotide having a 5-substituted-2-oxo(1H)-pyridin-3-yl group as a base. As is described in amended claim 2, the nucleoside or nucleotide of the present invention has a feature that the 5-position of the base is substituted with a substituent selected from the group consisting of the following:

1) a photoreactive group selected from iodine and bromine;

2) an alkenyl group, an alkynyl group or an amino group, or a derivative thereof;

3) biotin or a derivative thereof;

4) a fluorescent molecule selected from fluorescein, 6-carboxyfluorescein, tetramethyl-6-carboxyrhodamine, and derivatives thereof; and

5) biotin, dichloroacetyl group, fluorescein, 6- carboxyfluorescein, tetramethyl-6-carboxyrhodamine, or derivatives thereof introduced via a linker selected from an aminoalkyl group, an aminoalkenyl group and an aminoalkynyl group.

The base (5-substituted-2-oxo(1H)-pyridin-3-yl group) in the nucleoside or nucleotide of the present invention is a derivative of pyridin-2-one (y) wherein a functional component is attached to the 5' position of the base. The present nucleoside or nucleotide can be introduced into a specific position within DNA or RNA via artificial base pair(s) ("x-y" or "s-y") by using a template DNA wherein the artificial base "X" or "s" has been introduced.

Froehler *et al.* discloses oligonucleotides which are useful in oligonucleotide-based diagnosis and separation through triplex binding as is explicitly described in the "Abstract" thereof. Applicants note to the Examiner that that the artificial base disclosed in Froehler *et al.* cannot be introduced into DNA or RNA using polymerase. This fact is reported by Guo *et al.*, *"Inhibition of DNA Polymerase Reactions by Pyrimidine Nucleotide Analogues Lacking the 2-Keto Group,"Nucleic Acids Research, 1998, Vol.26, No.8. p.1863-1869* (Exhibit 1, enclosed).

In contrast, the present nucleoside or nucleotide can be enzymatically introduced into DNA or RNA via replication or transcription. This is demonstrated in the present application, in the examples. Specifically, in the present nucleoside or nucleotide, the base (5-substituted-2-oxo(1H)-pyridin-3-yl group) is attached to ribose or deoxyribose at its 3-position. The imino group at the 1-position in the base can form the hydrogen bond with the nitrogen atom at the 1-position in "X" or "s'. Further, the keto group at the 2-position in the base can form a hydrogen bond with the amino group at the 2-position in X" or "s". In this context, Applicants refer the Examiner to Figure 2 of the present invention.

The artificial base disclosed in Froehler *et al.* cannot form any hydrogen bond with "X" or "s'. There is no known artificial base which is complementary to the base of Froehler

et al. Further, the base does not have the keto group at the 2-position, and cannot be recognized by any polymerase (See Exhibit 1).

As previously discussed, in the first place, the object of Froehler *et al.* is clearly distinct from that of the present invention. In addition, the base of Froehler *et al.* cannot be introduced into DNA or RNA via replication or transcription. One of the important features of the present nucleoside or nucleotide is that the base (5-substituted-2-oxo(1H)-pyridin-3-yl group) is attached to ribose or deoxyribose at its 3-position. Froehler *et al.* does not describe or suggest the essential feature of the present invention.

The present nucleoside or nucleotide can be enzymatically introduced into DNA or RNA. Various functional groups described in the amended claim 2 can be introduced into the 5-position of the base, so as to enable production of various functional nucleic acids which have not existed before the present invention. For a better understanding of the present invention, Applicants refer the Examiner to a review article authored by one of the present inventors, Dr. Ichiro Hirao, which was published after the priority date of the present application (I. Hirao, *"Placing Extra Components Into RNA by Specific Transcription Using Unnatural Base Pair Systems,"* BioTechniques, *2006, Vol.40. No.6, p.711-717* (Exhibit 2, enclosed).

Based upon the above, and applying the *Graham factors* analysis test or a test described within the Guidelines, it is submitted that a *prima facie* case of obviousness has not been established as to the remaining claims. A conclusory statement indicating obviousness is not sufficient to support a *prima facie* case of obviousness. Therefore, in light of the above, it is submitted that the Examiner did not meet the standard for a *prima facie* case of obviousness.

Applicants respectfully request reconsideration and withdrawal of the present rejection.

Issues Regarding Information Disclosure Statement (IDS)

The Examiner indicated that references on the IDS dated January 14, 2005, were not considered due to the Examiner not having been provided copies of these references.

Applicants on this date are submitting the following references for consideration by the Examiner:

(1) WO 01/016149

(2) Ichiro HIRAO et al., Protein, Nucleic acid and Enzyme, Vol. 47, No. 14, pages 1904 to 1913 (November, 2002).

(3) I. HIRAO et al., Bioorganic & Medicinal Chemistry Letters, Vol. 12, pages 1391 to 1393, (May, 2002).

These references were listed on the International Search Report. As such, copies of the references should have been forwarded by the IB. However, additional copies are enclosed herewith for the Examiner's convenience.

The following reference, which was listed on the IDS dated January 14, 2005, was considered by the Examiner since it was supplied in the IDS dated June 15, 2007:

FUJIWARA et al., Bioorg. Med. Chem. Lett. Vol. 11, (2001), pages 2221-2223.

The following reference, which incorrectly listed the authors as I. HIRANO *et al.* on the IDS dated January 14, 2005, was considered by the Examiner since it was supplied in the IDS dated June 15, 2007 as:

HIRAO et al., Nature Biotechnol., Vol. 20, (2002), pages 177-182.

CONCLUSION

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Paul D. Pyla, Reg. No. 59, 228, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§ 1.16 or 1.14; particularly, extension of time fees.

Dated APR - 2 2008

Respectfully submitted,

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Attachments: Exhibit 1- Guo et al., "*Inhibition of DNA Polymerase Reactions by Pyrimidine Nucleotide Analogues Lacking the 2-Keto Group*," Nucleic Acids Research, 1998, Vol.26, No.8. p.1863-1869.

Exhibit 2- I. Hirao, "*Placing Extra Components Into RNA by Specific Transcription Using Unnatural Base Pair Systems*," BioTechniques, 2006, Vol.40. No.6, p.711-717 (Exhibit 2, enclosed).

GMM/PDP/kml